28. A method of treating osteoporosis comprising administering the intracellular domain of an isolated amino acid sequence of SEQ ID NO: 1 to a patient in need thereof.

29. The method of claim 28, wherein the patient is a human or another vertebrate.

REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

As correctly indicated in the Office Action Summary, claims 1-25 were pending in this application when last examined. Of the pending claims, claims 1 and 14-23 are rejected and claims 2-13, 24, and 25 stand withdrawn from consideration. The present Amendment cancels claims 20-23 without prejudice or disclaimer as to the canceled subject matter. Applicants reserve the right to file a continuation on any subject matter canceled by way of this amendment. The present Amendment also adds new claims 26-29. Accordingly, claims 1-19 and 24-29 are pending in this application.

Support for new claims 26-29 can be found, at least, in original claims 1 and 20-23. New claims 26-29 represent the subject matter of original claims 20-23 rewritten in independent form. Thus, no prohibited new matter is believed to be introduced by this Amendment.

I. Claim Objections

Claims 20-23 stand objected to under 37 C.F.R. § 1.75(c) as allegedly improper dependent claims for failing to further limit the subject matter of a previous claim. Office Action, Paper No. 14, page 7. Applicants note that the present amendment cancels claims

20-23 and adds new claims 26-29 as was suggested by the Examiner. The new claims represent the subject matter of original claims 20-23, but they have been rewritten in independent form. Thus, the rejection is mooted in view of the present amendment.

II. Rejections under 35 U.S.C. §§ 101 & 112, First Paragraph

Claims 1 and 14-23 stand rejected under 35 U.S.C. § 101, as purportedly lacking utility. As a consequence, claims 1 and 14-23 also stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to teach one of skill in the art how to use the claimed invention. Office Action, Paper No. 14, page 3. For at least all of the reasons set forth below, Applicants respectfully traverse these rejections and request their withdrawal.

To satisfy the utility requirement under 35 U.S.C. § 101, the claims and the specification must disclose either a credible "well-established utility" or a credible "asserted utility" for the claimed invention. M.P.E.P. § 2107.02. Applicants respectfully submit that the specification discloses both a credible "well-established utility" and a credible "asserted utility."

1. Well Established Utility

A "well established utility" is a specific, substantial, and credible utility that must be immediately apparent to one skilled in the art based on the characteristics of the invention (e.g., properties or applications of a product or process). M.P.E.P. § 2107; *Guidelines for Examination of Applications for Compliance With the Utility Requirement*, 66 Fed. Reg. 1097, 1098 (Jan. 5, 2001). In other words, it must be well known, immediately apparent and implied by the specification based on the disclosure of the properties of the claimed invention, either alone or taken with knowledge of one skilled in the art.

A review of the specification reveals that the specification more than satisfies the requirements for a "well established utility." To this end, the specification discloses a protein encoded by the HBM gene that has the property of causing elevated bone mass. Specification, page 17. In support of this asserted utility, the specification discloses a genetic linkage study for a family of HBM-affected individuals. Specification, page 31. The results of this analysis identify the gene responsible for the HBM phenotype as the mammalian LDL-receptor-related protein LRP5 with a single nucleotide polymorphism in the LRP5 gene resulting in an amino acid substitution at locus 171 (G to V) (hereinafter "G171V mutation" or "HBM gene"). Of the thousand individuals analyzed, it was discovered that this mutation was only present in the HBM-affected individuals. More importantly, it was discovered that the affected members of this large kindred have a much higher bone density than average, and yet still maintain normally shaped bones. The specification also teaches that peak skeletal mass is an important determinant of bone mass and is the principle measurable determinant of fracture risk. Specification, page 4. As a consequence, HBM-affected individuals are resistant to bone fracture, and older individuals in this family do not show the common loss of bone mass associated with normal aging. This study is strong evidence implicating the involvement of the claimed HBM gene and HBM protein in bone development.

To validate and investigate the G171V substitution and the HBM protein as being the cause of the human HBM phenotype, the specification further describes the construction of transgenic mice over-expressing the LRP5 G171V mutation in bone. These transgenic animals proved to be viable, healthy, and they exhibited the HBM trait that makes them resistant to bone fracture. Specification, page 91. These transgenic mice provide clear evidence that the protein plays a role in HBM development. These animals also afford a new model to explore compounds that may affect bone development.

In addition, the specification also provides Northern blot testing and PCR analysis suggesting that the protein is expressed in various human bone tissues, such as osteoblasts

of the proximal metaphysis, bone marrow, and calvarial bone. Figures 7A & 7B; Specification, page 76. Table 5 also indicates that the protein is expressed in proliferating chondrocytes in the growth plate. *In situ* hybridization studies to rat tibia using sense and antisense probes further confirm that the protein is expressed in various human bone tissues. Figures 10-13. Both the Northern blotting and the *in situ* hybridization reveal a high level of HBM protein expression in bone cells.

Taken together, these teachings indicate that the HBM gene and the HBM protein are responsible for the HBM phenotype, and are important in bone mineralization and development. Given the evidence that the HBM protein alters bone development, one skilled in the art would immediately recognize as a credible the use of the HBM protein to alter bone development. One skilled in the art would also find credible the use of the HBM protein in drug screening assays to find compounds that bind to it, thereby potentially altering bone development. Another credible well-established use includes the use of the HBM protein to diagnose individuals with the HBM phenotype. Therefore, the specification clearly discloses a credible "well-established utility." For this reason alone, the rejection should be withdrawn.

To confirm that these well established utilities are indeed credible, Applicants further provide: Gong et al., *LDL Receptor-Related Protein 5 (LRP5) Affects Bone Accrual and Eye Development*, CELL 107:513-523 (Nov. 16, 2001) (hereinafter "Gong"); the anonymous research abstract *Researchers Discover "Thermostat" that Regulates Bone Density*, Research News, HOWARD HUGHES MEDICAL INSTITUTE RESEARCH NEWS (Nov. 16, 2001), *available at* http://hhmi.org/news/warman.html; and Little et al., *A Mutation in the LDL Receptor-Related Protein 5 Gene Results in the Autosomal Dominant High-Bone Mass trait*, AM. J. HUM. GENET. 70:11-19 (2002) (hereinafter "Little").

The Gong article discloses six disease causing and frameshift mutations in LRP5 that are responsible for causing the inherited bone disorder, osteoporosis-pseudoglioma

syndrome (OPPG). Gong, page 515, Figure 2A. Gong indicates that people with this genetic disorder have a very low bone mass and are prone to developing fractures and deformation. In fact, Gong indicates that carriers of a mutation in LRP5 have half the normal complement of functional LRP5 resulting in the reduction in bone mass. Thus, this study confirms that LRP5 is involved in bone development.

The attached research abstract also discusses the role of LRP5 in bone development. In particular, it characterizes LRP5 as a "thermostat" that regulates bone density. Abstract, page 2. In reference to the Gong article, the abstract discusses the mutation in LRP5 that results in OPPG. The abstract further describes additional research indicating that a genetic trait in humans that causes higher-then-normal bone density also maps to the same genomic region in LRP5 and that this suggests "that enhancing the function of the LRP5-signaling pathway could increase bone density, not only in people suffering rare, severe bone disorders such as OPPG, but also for people with subtler deficiencies in bone mass." Abstract, page 2.

Finally, Little discusses the research done by the inventors of the current application. More specifically, this article describes the genetic linkage study for a family of HBM-affected individuals. The results of this analysis of over 1,000 individuals clearly identifies the specific G171V mutation in LRP5 as causing enhanced HBM protein expression resulting in the elevated bone mass phenotype.

Accordingly, these articles further confirm that the single G171V mutation in LRP5 is responsible for the HBM phenotype and that enhancing HBM expression results in elevated bone mass. In some respects, the HBM phenotype is analogous to cystic fibrosis in that both conditions are caused by a single point mutation. *See* Julian Zielenski, *Genotype and Phenotype,* RESPIRATION 67:177-133 (2000) (hereinafter "Zielenski"). Thus, one skilled in the art of human genetics and familial inheritance, upon reading the disclosure and in being knowledgeable about the state of the art as evidenced by the

provided references, would readily recognize and appreciate that the claimed invention does indeed have a credible well-established utility.

Hence, Applicants submit that the above discussion effectively rebuts the Examiner's assertion that the claimed invention lacks utility and enablement because it is allegedly unclear how a single mutation in an LRP protein could alter the course of a multi-factorial disease such as osteoporosis. Office Action, Paper 14, page 5.

2. **Specific Asserted Utility**

In addition to the credible well established utility described above, Applicants submit that the specification provides numerous "credible asserted utilities." A "specific asserted utility" is an explicit statement of "why the applicant believes that the invention is useful." M.P.E.P. § 2107.02. Such statements will usually explain the purpose of how the invention may be used. *Ibid.* A "substantial utility" defines a real world use. *Ibid.* Along these lines, ***only one*** credible assertion of specific and substantial utility for the claimed invention is necessary to satisfy the utility requirement. M.P.E.P. § 2107. Moreover, the ***threshold of utility is not high***. *See* Brenner v. Manson, 383 U.S. 519, 534 (1966) (Emphasis added). Thus, if the asserted specific and substantial utility is considered credible by one skilled in the art, a rejection based on lack of utility is inappropriate. M.P.E.P. § 2107.

Applicants submit that the specification provides at least the following specific and substantial credible asserted utilities regarding the claimed proteins and methods. For instance, the specification sets forth such uses as:

1. the use of the HBM protein in drug screening assays (*e.g.*, competitive binding assays) to find inhibitors, agonists, or antagonists of Zmax1 or HBM protein activity;

2. the use of the HBM protein as a therapeutic agent to alter the level of bone mineralization and thus treat osteoporosis;

3. the use of the HBM protein as a surrogate marker, i.e., as a diagnostic indication of a symptom or sign that can be observed in a cell, tissue or animal that is correlated with the HBM phenotype;

4. the use of the HBM protein in rational drug design studies to produce structural analogs having improved HBM protein activity or stability, or which act as inhibitors, agonists, antagonists of HBM; and

5. the use of the HBM protein to produce antibodies that can be used in diagnostic assays to screen for HBM expression;.

Applicants submit that any one of the above asserted utilities for the claimed invention would have been recognized as credible by those skilled in the art at the time of the claimed invention for at least the reasons set forth below.

Starting with the first, one skilled in the art would recognize as credible the use of the HBM protein in drug screening assays, such as competitive binding assays to find inhibitors, agonists, or antagonists of high bone mass activity. To this end, the specification teaches that the HBM protein is useful in a variety of drug screening assays, such as competitive binding assays, to identify inhibitors, agonists, and antagonists of HBM protein activity. For instance, the specification teaches that Zmax1 and the HBM protein are known to interact with several proteins, such as ApoE. Specification, pages 95-97 and 102. The specification indicates that compounds that inhibit the interaction between HBM and ApoE may be isolated using standard ligand-binding assays. This involves immobilizing HBM on a solid support, such as the base of a microtiter well, and adding for example both derivatized ApoE and a candidate compound to see if it specifically inhibits the interaction between ApoE and HBM. Candidate compounds that inhibit this binding would then be utilized in a variety of ways to alter bone development. Applicants submit that such screening assays are well known to one skilled in the art of pharmaceutical development. Applicants submit Kim et al., *A New Low Density Lipoprotein Receptor Related Protein, LRP5, Is Expressed in Hepatocytes and Adrenal Cortex, and Recognizes Apolipoprotein E*, J. BIOCHEM. 124:1072-1076 (Sept. 24, 1998) (hereinafter "Kim") as evidence that such assays are well known in the art. Kim describe a

ligand binding assay for LRP5 and ApoE utilizing CHO cells transfected with adenovirus containing LRP5. Kim at 1074, first column, 3rd paragraph. Binding activity was measured with fluorescent labels. Given that the HBM protein and the LRP5 protein share sequence identity, one of skill in the art would recognize as credible the use of the HBM protein in the same ligand binding assay for ApoE as disclosed in Kim.

As further evidence that such assays are well known in the art, Applicants submit Tamai et al., *LDL-receptor-related proteins in Wnt signal transduction*, NATURE 247:530-535 (Sept. 2000) (hereinafter "Tamai"). This article investigates the function of LRP6 as a co-receptor in Wnt signal transduction. In doing so, the investigators utilized numerous assays looking for LRP6 inhibitors. For instance, in one particular assay, investigators inhibited the function of endogenous LRP6 by injecting mutant LRP6 into blastomeres at the four-cell stage and then observed changes in neural crest development. Tamai at 532, second column, first paragraph. Clearly, such assays are simple and routine in the art. Tamai further demonstrates that such rudimentary techniques are applicable to LRP5 which shares 71% amino-acid identity to LRP6. Tamai at 531, second column, first paragraph.

Applicants note that the assays in the above-described journal articles are representative of the various assays that are common and routine in the art. Applicants further submit that one of skill in the art would immediately recognize the applicability of the claimed invention to this routine and common technology. Furthermore, since no evidence has been presented to contradict this credible asserted utility, let alone any of the specific asserted utilities described in the disclosure, one of skill in the art upon reading the disclosure would recognize as credible the use of the HBM protein in drug screening assays, such as competitive binding assays to find inhibitors, agonists, or antagonists of high bone mass activity.

Second, as to the claimed methods of altering bone development and treatment, the specification, as discussed above, discloses the results of linkage analysis and mutation

analysis which indicate that older individuals carrying the HBM gene express the HBM protein and that these individuals do not exhibit the loss of bone mass characteristic with old age. Consequently, these HBM carriers are not susceptible to diseases characterized by reduced bone density, such as osteoporosis. Specification, page 9, lines 21-26, page 31, lines 19-21. Such individuals are equivalent to individuals being treated with the HBM protein. Specification, page 86, lines 20-21. The results also indicate that the HBM affected individuals seem to be resistant to fractures. Specification, page 31, lines 5-10. Furthermore, the specification discloses that a transgenic mouse carrying the HBM gene is viable, healthy, and has elevated bone mass. Specification, page 91, lines 16-17. Additionally, as osteoporosis is generally recognized as a disease resulting from a loss of bone mass and the specification teaches that the HBM protein elevates bone mass, it follows that the administration of the HBM protein would alter bone development by elevating bone mass. Accordingly, in view of the above, one skilled in the art also would find credible the use of the claimed protein in methods for altering bone development and treating osteoporosis.

Third, Applicants note that one skilled in the art would recognize as credible the use of the HBM protein as a surrogate marker to confirm the presence of the elevated high bone mass phenotype in individuals. For instance, the specification, at pages 93 and 94, sets forth one example for identifying a surrogate marker for elevated bone mass using a pedigree of humans carrying the HBM gene. This process involves taking blood samples from individuals carrying the HBM gene and from individuals not carrying the gene. Such individuals can be identified from the genetic linkage studies. Proteins in the serum from these individuals are then electrophoresed on a two dimensional gel. Spots corresponding to proteins from HBM individuals are then identified and compared to those from normal individuals. Spots unique to HBM individuals are then isolated using antibodies specific for the HBM protein. Spots unique to HBM individuals correspond to those proteins that are useful as surrogate markers. The specification then describes diagnostic assays for HBM proteins using antibodies described in the specification. The specification then goes

on to describe how antibodies are made to the HBM protein. Specification, pages 101 and 102.

Applicants submit that the above techniques are common and routine in the art. Applicants also note that this technique is just one of many described in the specification regarding surrogate markers. The specification clearly demonstrates that the HBM gene results in individuals with the elevated bone mass phenotype that makes them more resistant to bone fracture. The specification also teaches that bone mass is a measurable determinant of fracture risk. From this, one of skill in the art would immediately recognize that the HBM protein has "real world" value as a surrogate marker to identify HBM individuals. Along these lines, Applicants note that M.P.E.P. 2107.01 states that

> ...an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventative measures or further monitoring.

Given that the use of the HBM protein as a surrogate marker is analogous to the above example described in the M.P.E.P. as a credible asserted utility, it is evident that at least one of the asserted specific utilities is credible. Thus, it would be inconsistent to maintain that the claimed invention lacks utility. Moreover, no evidence has been presented to contradict this specific asserted utility. Accordingly, one skilled in the art upon reading the disclosure would immediately recognize this specific asserted utility as credible.

Fourth the specification discloses that the HBM protein could be used in rational drug design studies to manufacture potential drugs (i.e., agonists, antagonists, inhibitors). Specification, pages 96-97. This approach involves determining the three-dimensional structure of the HBM protein using computer modeling and/or X-ray crystallography. The specification also indicates that this technology is common and routine in the art and that it was used in the development of HIV protease inhibitors. Specification, page 97. Accordingly, one of skill in the art would recognize as credible the use of the HBM in

rational drug design studies to design agonist, antagonists, or inhibitors for bone modulation.

Fifth, Applicants note that one skilled in the art would recognize as credible the use of the HBM protein to generate antibodies useful for detecting the HBM protein. The specification provides methods for detecting the HBM protein using antibodies specific to the HBM. To this end, the specification teaches that the HBM protein was used to generate antibodies useful for isolating the HBM protein. Specification, pages 85 and 86. It is well established that diagnostic antibodies are well known and widely used in the biotechnology industry. Likewise, the use of proteins in diagnostic assays to detect the presence of disease is also well known. No evidence has been presented to discredit this specific asserted utility.

Thus, the specification provides **several** asserted, specific and substantial credible utilities regarding the claimed proteins and methods. It is well established that such asserted utilities are ***presumed true***. M.P.E.P. § 2107.01 and *In re* Brana, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (Emphasis added). To overcome the presumptive truth of the asserted specific utilities set forth in the specification, the Office must show by a ***preponderance of evidence*** that it is ***more likely than not*** that the asserted specific utility would be considered false by a person of ordinary skill. M.P.E.P. § 2107.01 and *In re* Corkill, 226 U.S.P.Q. 1005, 1008 (Fed. Cir. 1985) (Emphasis added).

Applicants submit that the Office has failed to overcome this presumption because no evidence or arguments have been presented that specifically contradict the asserted utilities set forth in the specification and above. In other words, the Office has not shown by a preponderance of evidence that it is more likely than not that the asserted specific utilities would be considered false by a person of ordinary skill in the art. Instead, the Examiner relies on four basic arguments to support his rejection for lack of utility and the corresponding lack of enablement rejection.

First, the Examiner asserts that the treatment of bone development and osteoporosis is unpredictable due to the multi-factorial nature of the disease. Office Action, Paper No. 14, page 5. The Examiner also believes that the specification fails to disclose a specific function of the HBM protein (i.e., effect on osteoclast or osteoblast activity) in the development of the HBM phenotype. Similarly, the Examiner alleges that the specification fails to disclose whether the HBM phenotype is the result of the loss of Zmax1 protein activity or is the result of altered Zmax1 protein function due to a mutation in the Zmax1 gene. Office Action, Paper No. 14, page 7.

Applicants respectfully traverse this rejection and submit that the specification need not disclose the HBM protein's effect on any particular cell type to be effective as claimed, because the specification makes it clear that HBM affected individuals express the HBM protein and have an elevated bone mass. This elevated bone mass makes them more resistant to fractures. Thus, it follows that such HBM-affected individuals are not susceptible to diseases such as osteoporosis regardless of HBM's effect on any particular cell type. Nonetheless, contrary to the Examiner's assertion otherwise, the specification does indicate that HBM is expressed in certain particular cells, such as osteoclasts or osteoblasts. See, for example Figures 10-13. Furthermore, the specification makes it clear that the HBM phenotype is the result of altered expression of the protein, as opposed to a loss of a function of Zmax1.

Second, the Examiner alleges that specification is not enabled for altering bone development, because the HBM protein is related to the low density lipoprotein receptor that was previously known to only play a key role in the hepatic clearance of cholesterol carrying LDL. Office Action, Paper 14, page 5. However, the similarity between the proteins ***does not*** negate the evidence provided in the specification that individuals expressing the HBM protein are protected from diseases such as osteoporosis. If anything, this only suggests the surprising and unexpected findings of the claimed invention.

Third, the Examiner alleges that the specification is not enabled due to the lack of a working example. It is well established that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether a working example is disclosed. Instead, the specification need not contain an example, if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without undue experimentation. *In re* Borkowski, 422 F.2d 904, 908, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970); M.P.E.P. § 2164.02. Nonetheless, Applicants submit that the evidence (i.e., familial data, antisense data, transgenic animal studies, *in situ* hybridization studies, etc.) makes clear that the HBM protein elevate bone mass and thus protects individuals from bone-related diseases.

Fourth, the Examiner asserts that the specification is not enabled, because the specification allegedly fails to disclose how to purify the receptor in its active form and to effectively administer it. However, it is well established that a specification need not teach, and preferably omits, what is well known in the arts. *In re* Buchner, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991), and M.P.E.P. § 2164.01. Nonetheless, the specification describes numerous methods for the expression of the claimed HBM protein. Specification, section on Protein Expression and Purification, pages 81-86. The specification at page 76 and at Figures 6A-6E also describes the three-dimensional structure of the extracellular domain of Zmax1, as well as the exact location of the G171V mutation within the extracellular domain. Given this information, one of skill in the art could easily purify the extracellular domain of the receptor without undue experimentation.

In addition, a specification need not specify the dosage or method of use if it is known that one skilled in the art could obtain such information without undue experimentation. For instance, one of skill in the art would be able to discern an appropriate dosage or method of use without undue experimentation based on knowledge of compounds having similar physiological or biological activity. M.P.E.P. § 2164.01(c). In the instant case, the specification discloses other treatments for osteoporosis, such as

estrogen replacement therapy (*e.g.*, raloxifene and tamoxifene). Accordingly, in light of these other therapies, one of skill in the art would be able to ascertain the appropriate dosages without undue experimentation.

In view of the above, it is evident that at least one of the asserted specific utilities discussed in detail above is credible. Applicants submit that no evidence has been provided which negates the credibility of any of the asserted utilities let alone all of the utilities. In the absence of any scientific evidence or apparent reasons why the claimed compounds do not possess the disclosed specific utilities, the allegation of utility in the specification must be accepted as correct. *In re* Kamal, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968). Certainly, the Office has not provided evidence that ***all*** the asserted specific utilities would be reasonably doubted, are inherently unbelievable or involve implausible scientific principles. Therefore, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 101. Applicants further submit that in view of the above, the rejection under 35 U.S.C. § 112, first paragraph should also be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly requested.

In the event that there are any questions relating to this Amendment and Reply, or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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